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Experience with Replacement Therapy in the Destructive Lung Disease Associated with Severe Alpha-1-Antitrypsin Deficiency[1,2]

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Studies over the past 20 years have fostered a dramatic improvement in our understanding of the disease mechanisms underlying pulmonary emphysema. It is fitting that the "experiment in nature" that provided the foundation for the protease theory of emphysema should provide the initial opportunity to translate these pathogenetic insights into specific therapy (1). In the interim since the landmark observation by Laurell and Erickkson (2), studies performed in a number of laboratories have served to demonstrate the relevance of serum alpha-1-antitrypsin deficiency to the destruction of alveolar structures. Most importantly, it is now recognized that: (*1*) neutrophil elastase is inhibited by alpha-1-antitrypsin (3); (*2*) experimental destructive lung disease can be produced by human neutrophil elastase (4, 5); (*3*) the risk of developing destructive lung disease is directly related to the severity of the alpha-1-antitrypsin serum deficiency (i.e., the PiZ phenotype of alpha-1-antitrypsin is the phenotype most commonly associated with premature emphysema and, with rare exception, the PiZ phenotype is also associated with the lowest serum levels) (6); (*4*) individuals with the PiZ form of alpha-1-antitrypsin deficiency are devoid of effective inhibitory activity against neutrophil elastase at the level of their alveolar structures (7); and (*5*) PiZ patients with destructive lung disease have a chronic influx of neutrophils (8). Together, these observations strongly support the concept that the lung destruction associated with alpha-1-antitrypsin deficiency results from the unimpeded action of neutrophil elastase on the alveolar structures.

In this context, it is reasonable to propose that, like other serum protein deficiencies such as inherited hypogammaglobulinemia (9), hemophilia (10), and hereditary angioedema (11), alpha-1-antitrypsin deficiency could be corrected by parenteral replacement therapy. However, there are several formidable obstacles that must be overcome before alpha-1-antitrypsin therapy becomes a reality.

Most importantly, the expression of destructive lung disease in alpha-1-antitrypsin deficiency is an insidious, progressive loss of lung function that culminates in respiratory failure over a period ranging from several years to a decade or more (12). This implies a requirement for continuous maintenance replacement therapy beginning early in the course of the disease. In contrast, the use of factor VIII preparations in hemophilia and C1-inhibitor preparations in hereditary angioedema can be timed to provide control of readily observable expressions of disease, e.g., bleeding and mucosal edema, respectively. Whereas long-term maintenance replacement therapy is used for the control of recurrent infections in hypogammaglobulinemic patients, this has proven feasible because immunoglobulin G has a serum half-life of approximately 30 days in humans (9). In contrast, studies of the metabolism of alpha-1-antitrypsin in man have shown that it possesses a half-life of only 4 to 5 days (13). Taken together, these data suggest that successful parenteral replacement therapy of alpha-1-antitrypsin deficiency would require large amounts of alpha-1-antitrypsin given at frequent intervals to assure continuous protection of the alveolar structure in the deficient individual. In addition, safe and effective alpha-1-antitrypsin replacement would require a preparation of the antiprotease that would: (*1*) have access to the target organ, i.e., the lung; (*2*) retain its biologic activity; (*3*) be sterile and pyrogen-free; (*4*) be devoid of serum components likely to produce adverse reactions when administered intravenously (e.g., aggregates of IgG); and, (*5*) offer an acceptable margin of safety with regard to the risk of transfusion hepatitis (14).

As a necessary concession to the stringent requirements imposed by the biology of alpha-1-antitrypsin, we approached the problem of replacement therapy by partially purifying the protein for use in replacement therapy by sequential polyethylene glycol precipitation of pooled normal plasma (14). This approach permits the recovery of approximately 80% of the alpha-1-antitrypsin in the 20- to 40% polyethylene glycol fraction of the plasma. Rapid processing allows the preparation of an alpha-1-antitrypsin concentrate that is sterile and pyrogen-free while retaining its full antiprotease activity. The initial treatment of the pooled plasma with 20% polyethylene glycol results in the removal of aggregates of IgG, high molecular weight kininogen, and complement components C1, C4, C2, C3, and C5. In addition, this form of precipitation in polyethylene glycol confers a desirable margin of safety with regard to the risk of transfusion hepatitis, because hepatitis B virus is removed from the alpha-1-antitrypsin fraction under these conditions. The final alpha-1-antitrypsin concentrate represents a 3-fold enrichment of the antiprotease. Importantly, this enrichment was attained without resorting to large scale chromotographic procedures with the attendant risk of contamination with bacterial products. The 20- to 40% concentrate is sterilized by microfiltration and can be stored for up to two weeks prior to use in intravenous replacement therapy.

The goals of our initial studies of parenteral alpha-1-antitrypsin replacement have been directed toward objective evidence of reversal of the protease-antiprotease imbalance within the PiZ lung; i.e., if there is any promise in the specific therapy of this disease, it is logical to hypothesize that parenteral replacement therapy must reestablish protease-antiprotease balance at the level of the lower respiratory tract when administered at reasonable intervals.

In order to attain a level of the serum antiprotease similar to that of normal individuals, the patients with the PiZ phenotype would require nearly tenfold increase in

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their serum alpha-1-antitrypsin levels. However, analysis of the epidemiology of destructive lung disease associated with the inheritance of "intermediate" forms of alpha-1-antitrypsin levels has shown that levels in the range of 50% of normal (e.g., PiMZ phenotype) possess a minimal risk for the devleopment of disease (15). By contrast, individuals with the PiSZ phenotype have serum alpha-1-antitrypsin levels in the range of 30 to 35% of normal and clearly have an increased risk of destructive lung disease. Thus, it is logical to hypothesize that serum alpha-1-antitrypsin values in the range of 35- to 50% of normal is all that is necessary to maintain adequate protease-antiprotease balance at the level of the alveolar structures. In this context, we designed our replacement therapy based on the known extracellular distribution of alpha-1-antitrypsin and its catabolic rate (13) in order to maintain serum and lung levels in this theoretical protective range. To accomplish this, 4 g of alpha-1-antitrypsin were administered intravenously every 7 days for 4 consecutive weeks. Documentation of the biochemical effects of the replacement therapy was provided by analysis of bronchoalveolar lavage fluid obtained before therapy and again following the second and fourth infusion of the alpha-1-antitrypsin concentrate.

Results and Discussion

Five individuals with severe alpha-1-antitrypsin deficiency (PiZ phenotype; mean serum alpha-1-antitrypsin levels of 37 ± 4 mg/dl) and advanced destructive lung disease were enrolled in the replacement therapy study (14). The alpha-1-antitrypsin levels were increased from mean pretreatment values of 37 ± 4 mg/dl to 108 ± 12 mg/dl at 2 days following the intravenous infusion of 4 g of alpha-1-antitrypsin. There were commensurate increases in serum antielastase activity. Thus, each of the study patients demonstrated the anticipated increment in functional and antigenic serum alpha-1-antitrypsin levels following the weekly infusions.

Whereas serum alpha-1-antitrypsin levels fell progressively during the 7-day interval between infusions, the weekly infusion schedule maintained levels in a range at or above 35% of normal levels. This implies that serum levels of alpha-1-antitrypsin necessary to protect the alveolar structures can be maintained with this replacement schedule.

More importantly, the use of intravenous alpha-1-antitrypsin administration resulted in a restoration of antiprotease balance at the level of the lung in these PiZ subjects. Bronchoalveolar lavage analysis prior to therapy demonstrated an absence of functional antielastase activity, in keeping with alpha-1-antitrypsin levels that were less than 5 μg/mg albumin (normal values; 51 ± 10 μg/mg albumin) (7, 14). In contrast, two days following the intravenous administration of four g of alpha-1-antitrypsin, lower respiratory tract alpha-1-antitrypsin levels increased to approximately 60% of normal along with the appearance of an equivalent quantity of functional antielastase activity. In addition, whereas active elastase activity was recovered from the lower respiratory tract prior to the initiation of replacement therapy, the infusion of alpha-1-antitrypsin concentrate abolished the free elastase activity within the alveolar structures of these individuals (8). Thus, the use of bronchoalveolar lavage to monitor the effects of replacement therapy demonstrated that parenteral administration of alpha-1-antitrypsin restored protease-antiprotease balance at the level of the lung in PiZ patients. These findings suggest that it is feasible to interrupt the proteolytic processes operative in the pathogenesis of this lung disease by weekly administrations of an alpha-1-antitrypsin concentrate readily obtained from pooled human plasma (8, 14).

Experience with this alpha-1-antitrypsin preparation also demonstrated the safety of this approach to replacement therapy. There were no significant untoward reactions to the infusion of the alpha-1-antitrypsin concentrate. The use of carefully screened volunteer plasma coupled with the 20% polyethylene glycol precipitation appear to provide a desirable margin of safety with regard to the risk of transfusion hepatitis. None of the patients in this study developed clinical or biochemical evidence of hepatitis following the infusion of this plasma fraction (14).

The next step in the evaluation of replacement therapy in alpha-1-antitrypsin deficient emphysema is the application of this approach to long-term clinical studies. Before replacement therapy can be accepted for routine use in this disorder, studies are necessary to demonstrate that the PiZ phenotype will result in conservation of lung function and an improved clinical outcome in alpha-1-antitrypsin deficient individuals. Although such a study will be fraught with difficulty regarding selection of patients and clinical end-points, it will also provide a unique opportunity to test directly the relevance of the proteolytic theory of the pathogenesis of emphysema.

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